GensiaSicor™
PHARMACEUTICALS
A GensiaSicor Company

January 4, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

RE: ANDA Suitability Petition
Thiotepa for Injection, USP

ANDA Suitability Petition

The undersigned submits this Suitability Petition (the "Petition") under the provisions of the Federal Food, Drug and Cosmetic Act, Section 505(j)(2)(c) and 21 CFR 314.93 to request the Commissioner of Food and Drugs to allow submission of an abbreviated new drug application (ANDA) for Thiotepa for Injection in a strength of 30 mg/vial.

A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs permits a change in the total drug content (strength) to allow for submission of an abbreviated new drug application (ANDA) for Thiotepa for Injection in a strength of 30 mg/vial. The basis of the Petition is the reference listed drug product, Thioplex®, marketed by the innovator, Immunex Corporation, which is available as 15 mg/vial. Immunex Corporation received approval of NDA 20-058 on December 22, 1994, for the Thioplex® 15 mg/vial product.

B. Statement of Grounds

The subject of the Petition for Thiotepa for Injection is to permit a change in the total drug content (strength). The reference listed drug product, Thioplex®, marketed by the

00P-0092 CP1

Gensia Sicor Pharmaceuticals, Inc. • 19 Hughes • Irvine CA • 92618-1902 • USA
Phone (949) 455-4700, (800) 729-9991 • Fax (949) 855-8210 • http://www.gensiasicor.com

innovator, Immunex Corporation, is available as a 15 mg/vial. Immunex Corporation received approval of NDA 20-058 on December 22, 1994, for the Thioplex® 15 mg/vial product.

Gensia Sicor's proposed drug product will be packaged in a single use vial at the same concentration, 10 mg/mL when reconstituted, as the reference listed drug product, but in a different strength of 30 mg/vial.

Product	Dosage Form	Route of Administration	Drug Concentration	Strength
INNOVATOR'S Thioplex®	Sterile Solution	Intravenous Intracavitary Intravesical	10 mg/mL	15 mg/vial
(Proposed) GENSIA SICOR'S Thiotepa	Sterile Solution	Intravenous Intracavitary Intravesical	10 mg/mL	30 mg/vial

The proposed larger vial size will provide fewer vials to reconstitute in order to attain the required dosages, thereby, decreasing dosage preparation error and of product exposure to personnel. In addition, the increased total dosage amounts offer a more cost-efficient product and decreases product inventory which benefits both the Health Care Facility and ultimately the patient. The subject drug is intended for use only as described in the **Indications** and **Dosage and Administration** sections of the package insert appended in the side-by-side comparison of the proposed labeling for Gensia Sicor's Thiotepa for Injection and Immunex's Thioplex® in **Attachment 1**. To support this petition, a Medical Rationale for the proposed product strength is provided in **Attachment 2**.

Appended in **Attachment 3** is the package insert for Thioplex®, Immunex Corporation. The labeling for the proposed drug is essentially identical to that of Immunex's Thioplex®, but differs only with respect to the description of the product, product name, the how-supplied statement, and the specific manufacturer's information.

C. Environmental Impact

In accord with 21 CFR 25.24(c)(1), an Environmental Impact Analysis Statement is not required if there is a determination that Thiotepa for Injection is suitable for ANDA status.

D. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

We trust you will find the information in the Petition to be satisfactory for your review and approval. Should you have any questions or require further clarification, please contact me at (949) 457-2808.

Sincerely,

Rosalie A. Lowe

Rosalie A. Lowe
Associate Director, Regulatory Affairs

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1 Side-by-Side Comparison of the Proposed Labeling vs. Immunex's Thioplex®

2 Medical Rationale

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Attachment 1

Side-by-Side Comparison of the Proposed Labeling Gensia Sicor's Thiotepa for Injection Vs. Immunex's Thioplex®

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

Y36-100-911
Package Insert

GensiaSicor® PHARMACEUTICALS

1

$R_x only$

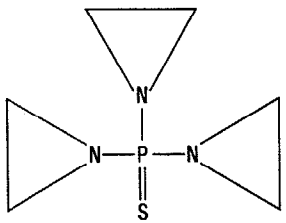
Thiotepa
for Injection, USP

DESCRIPTION

2 Thiotepa for injection is an ethylenimine-type compound. It is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous, intracavitary or intravesical 3 administration, containing 15 mg and 30 mg of thiotepa. Thiotepa is a synthetic product with antitumor activity. The chemical name for thiotepa is Aziridine, 1,1',1"-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide. 4

Thiotepa has the following structural formula:

5



Thiotepa has the empirical formula $C_6H_{12}N_3PS$ and a molecular weight of 189.22. When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5-7.5. Thiotepa is stable in alkaline medium and unstable in acid medium.

S00000S

Immunex

6

THIOPLEX®
(Thiotepa For Injection)
15 mg/Vial

DESCRIPTION

THIOPLEX® (thiotepa for injection) is an ethylenimine-type compound. It is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous, intracavitary or intravesical administration, containing 15 mg of thiotepa. THIOPLEX is a synthetic product with antitumor activity. The chemical name for thiotepa is Aziridine, 1,1',1"-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide.

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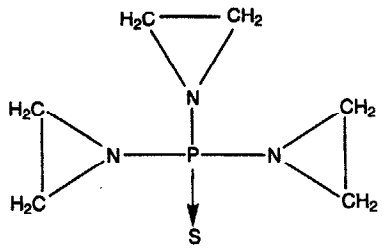

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1. Revised to Gensia Sicor's part number and product name; and to include "Package Insert," Gensia Sicor logo and Rx only symbol.
2. Revised to read "Thiotepa for injection."
3. Revised to include "...and 30 mg..."
4. Revised to read "Thiotepa."
5. Updated structural formula to current USP.
6. Revised to remove Bar Code from this location.

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

CLINICAL PHARMACOLOGY

Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines.

The pharmacokinetics of thiotepa and TEPA in thirteen female patients (45 - 84 years) with advanced stage ovarian cancer receiving 60 mg and 80 mg thiotepa by intravenous infusion on subsequent courses given at 4-week intervals are presented in the following table:

Pharmacokinetic Parameters	Mean ±SEM			
	Thiotepa		TEPA	
(units)	60 mg	80 mg	60 mg	80 mg
Peak Serum concentration (ng/mL)	1331 ± 119	1828 ± 135	273 ± 46	353 ± 46
Elimination half-life (h)	2.4 ± 0.3	2.3 ± 0.3	17.6 ± 3.6	15.7 ± 2.7
Area under the curve (ng/h/mL)	2832 ± 412	4127 ± 668	4789 ± 1022	7452 ± 1667
Total body clearance (mL/min)	446 ± 63	419 ± 56		

TEPA, which possesses cytotoxic activity, appears to be the major metabolite of thiotepa found in human serum and urine. Urinary excretion of ^{14}C-labeled thiotepa and metabolites in a 34-year old patient with metastatic carcinoma of the cecum who received a dose of 0.3 mg/kg intravenously was 63%. Thiotepa and TEPA in urine each accounts for less than 2% of the administered dose.

The pharmacokinetics of thiotepa in renal and hepatic dysfunction patients have not been evaluated. Possible pharmacokinetic interactions of thiotepa with any concomitantly administered medications have not been formally investigated.

INDICATIONS AND USAGE

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

Immunex

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No changes.

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

CONTRAINDICATIONS

1 Thiotepa is contraindicated in patients with a known hypersensitivity (allergy) to this preparation.

Therapy is probably contraindicated in cases of existing hepatic, renal, or bone-marrow damage. However, if the need outweighs the risk in such patients, thiotepa may be used in low dosage, and accompanied by hepatic, renal and hemopoietic function tests.

WARNINGS

Death has occurred after intravesical administration, caused by bone-marrow depression from systematically absorbed drug.

Death from septicemia and hemorrhage has occurred as a direct result of hematopoietic depression by thiotepa.

Thiotepa is highly toxic to the hematopoietic system. A rapidly falling white blood cell or platelet count indicates the necessity for discontinuing or reducing the dosage of thiotepa. Weekly blood and platelet counts are recommended during therapy and for at least 3 weeks after therapy has been discontinued.

Thiotepa can cause fetal harm when administered to a pregnant woman. Thiotepa given by the intraperitoneal (IP) route was teratogenic in mice at doses ≥1 mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose (0.8 mg/kg, 27 mg/m^2), based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses ≥3 mg/kg (21 mg/m^2), approximately equal to the maximum recommended human therapeutic dose, based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately two times the maximum recommended human therapeutic dose based on body-surface area.

Effective contraception should be used during thiotepa therapy if either the patient or partner is of childbearing potential. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.

Thiotepa is a polyfunctional alkylating agent, capable of cross-linking the DNA within a cell and changing its nature. The replication of the cell is, therefore, altered, and thiotepa may be described as mutagenic. An *in vitro* study has shown that it causes chromosomal aberrations of the chromatid type and that the frequency of induced aberrations increases with the age of the subject.

Like many alkylating agents, thiotepa has been reported to be carcinogenic when administered to laboratory animals. Carcinogenicity is shown most clearly in studies using mice, but there is some evidence of carcinogenicity in man. In patients treated with thiotepa, cases of myelodysplastic syndromes and acute non-lymphocytic leukemia have been reported.

Immunex

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PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

PRECAUTIONS

General

The serious complication of excessive thiotepa therapy, or sensitivity to the effects of thiotepa, is bone-marrow depression. If proper precautions are not observed thiotepa may cause leukopenia, thrombocytopenia, and anemia.

Information For Patients

The patient should notify the physician in the case of any sign of bleeding (epistaxis, easy bruising, change in color of urine, black stool) or infection (fever, chills) or for possible pregnancy to patient or partner.

Effective contraception should be used during thiotepa therapy if either the patient or the partner is of childbearing potential.

Laboratory Tests

The most reliable guide to thiotepa toxicity is the white blood cell count. If this falls to 3000 or less, the dose should be discontinued. Another good index of thiotepa toxicity is the platelet count; if this falls to 150,000, therapy should be discontinued. Red blood cell count is a less accurate indicator of thiotepa toxicity. If the drug is used in patients with hepatic or renal damage (see **CONTRAINDICATIONS** section), regular assessment of hepatic and renal function tests are indicated.

Drug Interactions

It is not advisable to combine, simultaneously or sequentially, cancer chemotherapeutic agents or a cancer chemotherapeutic agent and a therapeutic modality having the same mechanism of action. Therefore, thiotepa combined with other alkylating agents such as nitrogen mustard or cyclophosphamide or thiotepa combined with irradiation would serve to intensify toxicity rather than to enhance therapeutic response. If these agents must follow each other, it is important that recovery from the first agent, as indicated by white blood cell count, be complete before therapy with the second agent is instituted.

Other drugs which are known to produce bone- marrow depression should be avoided.

Carcinogenesis, Mutagenesis And Impairment Of Fertility

Also see **WARNINGS** section.

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Immunex

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Carcinogenesis, Mutagenesis and Impairment of Fertility

Also see **WARNINGS** section.

No changes.

PACKAGE INSERT--Part # Y36-100-911

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Gensia Sicor

Carcinogenesis

In mice, repeated IP administration of thiotepa (1.15 or 2.3 mg/kg three times per week for 52 or 43 weeks, respectively) produced a significant increase in the combined incidence of squamous-cell carcinomas of the skin, preputial gland, and ear canal, and combined incidence of lymphoma and lymphocytic leukemia. In other studies in mice, repeated IP administration of thiotepa (4 or 8 mg/kg three times per week for 4 weeks followed by a 20-week observation period or 1.8 mg/kg three times per week for 4 weeks followed by a 35-week observation period) resulted in an increased incidence of lung tumors. In rats, repeated IP administration of thiotepa (0.7 or 1.4 mg/kg three times per week for 52 or 34 weeks, respectively) produced significant increases in the incidence of squamous-cell carcinomas of the skin or ear canal, combined hematopoietic neoplasms, and uterine adenocarcinomas. Thiotepa given intravenously (IV) to rats (1 mg/kg once per week for 52 weeks) produced an increased incidence of malignant tumors (abdominal cavity sarcoma, lymphosarcoma, myelosis, seminoma, fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma, pheochromocytoma) and benign tumors.

The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m^2) is approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area. The lowest reported carcinogenic dose in rats (0.7 mg/kg, 4.9 mg/m^2) is approximately 6-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Mutagenesis

Thiotepa was mutagenic in *in vitro* assays in *Salmonella typhimurium*, *E. coli*, Chinese hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed *in vitro* with thiotepa in bean root tips, human lymphocytes, Chinese hamster lung, and monkey lymphocytes. Mutations were observed with oral thiotepa in mouse at doses >2.5 mg/kg (8 mg/m^2). The mouse micronucleus test was positive with IP administration of >1 mg/kg (3.2 mg/m^2). Other positive *in vivo* chromosomal aberration or mutation assays included *Drosophila melanogaster*, Chinese hamster marrow, murine marrow, monkey lymphocyte, and murine germ cell.

Impairment Of Fertility

Thiotepa impaired fertility in male mice at PO or IP doses ≥0.7 mg/kg (2.24 mg/m^2), approximately 12-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa (0.5 mg) inhibited implantation in female rats when instilled into the uterine cavity. Thiotepa interfered with spermatogenesis in mice at IP doses ≥0.5 mg/kg (1.6 mg/m^2), approximately 17-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa interfered with spermatogenesis in hamsters at an IP dose of 1 mg/kg (4.1 mg/m^2), approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Pregnancy

Category D: See **WARNINGS** section.

Immunex

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Category D: See **WARNINGS** section.

No changes.

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

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Nursing Mothers

It is not known whether thiotepa is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for thiotepa in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In addition to its effect on the blood-forming elements (see **WARNINGS** and **PRECAUTIONS** sections), thiotepa may cause other adverse reactions.

General: Fatigue, weakness. Febrile reaction and discharge from a subcutaneous lesion may occur as the result of breakdown of tumor tissue.

Hypersensitivity Reactions: Allergic reactions - rash, urticaria, laryngeal edema, asthma, anaphylactic shock, wheezing.

Local Reactions: Contact dermatitis, pain at the injection site.

Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

Renal: Dysuria, urinary retention. There have been rare reports of chemical cystitis or hemorrhagic cystitis following intravesical, but not parenteral administration of thiotepa.

Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of thiotepa and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Neurologic: Dizziness, headache, blurred vision.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

Immunex

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Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

Renal: Dysuria, urinary retention. There have been rare reports of chemical cystitis or hemorrhagic cystitis following intravesical, but not parenteral administration of thiotepa.

Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of thiotepa and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Neurologic: Dizziness, headache, blurred vision.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

No changes.

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

Special Senses: Conjunctivitis.

Reproductive: Amenorrhea, interference with spermatogenesis.

OVERDOSAGE

Hematopoietic toxicity can occur following overdose, manifested by a decrease in the white cell count and/or platelets. Red blood cell count is a less accurate indicator of thiotepa toxicity. Bleeding manifestations may develop. The patient may become more vulnerable to infection, and less able to combat such infection.

Dosages within and minimally above the recommended therapeutic doses have been associated with potentially life-threatening hematopoietic toxicity. Thiotepa has a toxic effect on the hematopoietic system that is dose related.

Thiotepa is dialyzable.

There is no known antidote for overdosage with thiotepa. Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

DOSAGE AND ADMINISTRATION

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally.

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Preparation and Administration Precautions: Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

Immunex

Special Senses: Conjunctivitis.

Reproductive: Amenorrhea, interference with spermatogenesis.

OVERDOSAGE

Hematopoietic toxicity can occur following overdose, manifested by a decrease in the white cell count and/or platelets. Red blood cell count is a less accurate indicator of thiotepa toxicity. Bleeding manifestations may develop. The patient may become more vulnerable to infection, and less able to combat such infection.

Dosages within and minimally above the recommended therapeutic doses have been associated with potentially life-threatening hematopoietic toxicity. Thiotepa has a toxic effect on the hematopoietic system that is dose related.

Thiotepa is dialyzable.

There is no known antidote for overdosage with thiotepa. Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

DOSAGE AND ADMINISTRATION

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered orally.

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Preparation and Administration Precautions: Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

000011

No changes.

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

1 **Preparation of Solution:** Thiotepa for injection 15 mg/vial and 30 mg/vial should be reconstituted with **1.5 mL and 3.0 mL**, respectively, of Sterile Water for Injection resulting in a drug concentration of approximately **10 mg/mL**. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

Label Claim (mg/vial)	Actual Content (mg/vial)	Amount of Diluent to be Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Withdrawable Amount (mg/vial)	Approximate Reconstituted Concentration (mg/mL)
15.0	15.6	1.5	1.4	14.7	10.4
30.0	31.2	3.0	2.8	29.4	10.4

2

The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% sodium chloride) before use.

When reconstituted with Sterile Water for Injection, solutions of thiotepa should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately. 3

In order to eliminate haze, solutions should be filtered through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

*Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®-GS Filter Unit).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: Thiotepa may be given by rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 - 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Immunex

Preparation of Solution: THIOPLEX (thiotepa for injection) should be reconstituted with **1.5 mL** of Sterile Water for Injection resulting in a drug concentration of approximately **10 mg/mL**. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

Label Claim (mg/vial)	Actual Content (mg/vial)	Amount of Diluent to be Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Withdrawable Amount (mg/vial)	Approximate Reconstituted Concentration (mg/mL)
15.0	15.6	1.5	1.4	14.7	10.4

The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% sodium chloride) before use.

When reconstituted with Sterile Water for Injection, solutions of THIOPLEX should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately.

In order to eliminate haze, solutions should be filtered through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

*Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®-GS Filter Unit).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: Thiotepa may be given by rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 - 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

1. Revised to read "Thiotepa for injection 15 mg/vial and 30 mg/vial should be reconstituted with **1.5 mL and 3.0 mL**, respectively."
2. Revised to include 30 mg/vial dosing information in table.
3. Revised to read "thiotepa."

PACKAGE INSERT--Part # Y36-100-911

Gensia Sicor

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Thiotepa for injection, for single use only, is available in vials containing 15 mg and 30 mg of non-pyrogenic, sterile lyophilized powder, supplied as follows:

1

NDC Number	Available Packaging
NDC 0703-**4301-02**	15 mg/vial, packaged 5 vials per shelf pack
NDC 0703-**4303-01**	30mg/vial, packaged Individually

Store in refrigerator between 2-8°C (36-46°F). PROTECT FROM LIGHT AT ALL TIMES.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal For Clinicians*. Sept/Oct 1983; 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.

2 Issued: February 1999
Gensia Sicor Pharmaceuticals, Inc
Irvine, CA 92618

3

Immunex

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

THIOPLEX® (thiotepa for injection), for single use only, is available in vials containing 15 mg of non-pyrogenic, sterile lyophilized powder, supplied as follows:

NDC 58406-661-31 - 6 x 15 mg/vial

STORAGE

Store in refrigerator between 2-8°C (36-46°F). PROTECT FROM LIGHT AT ALL TIMES.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal for Clinicians*. Sept/Oct 1983; 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.

4 immunex®

Manufactured for IMMUNEX CORPORATION, Seattle, WA 98101
by LEDERLE PARENTERALS, INC., Carolina, Puerto Rico 00987

Rev 0167-00
40768-94 (IM1)

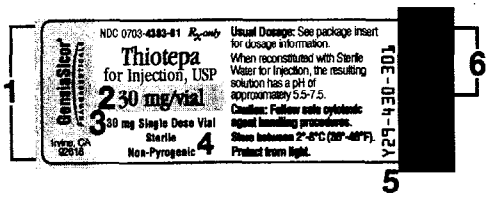
Issued 12/94

000013

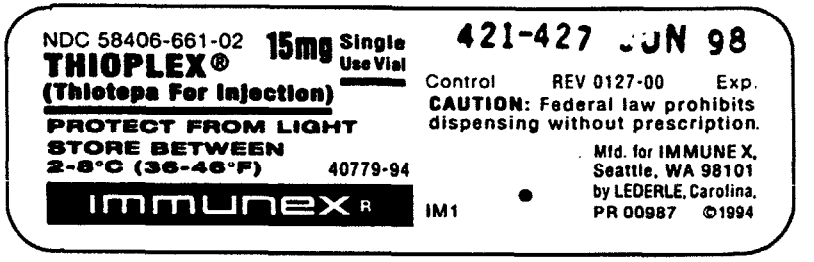
1. Revised to Gensia Sicor's **"How Supplied"** information.
2. Revised to Gensia Sicor's issue date, company name and address.
3. Revised to include Gensia Sicor's bar code.
4. Removed Immunex logo.

5 mL VIAL LABEL--Part # Y29-430-301

Gensia Sicor



Immunex

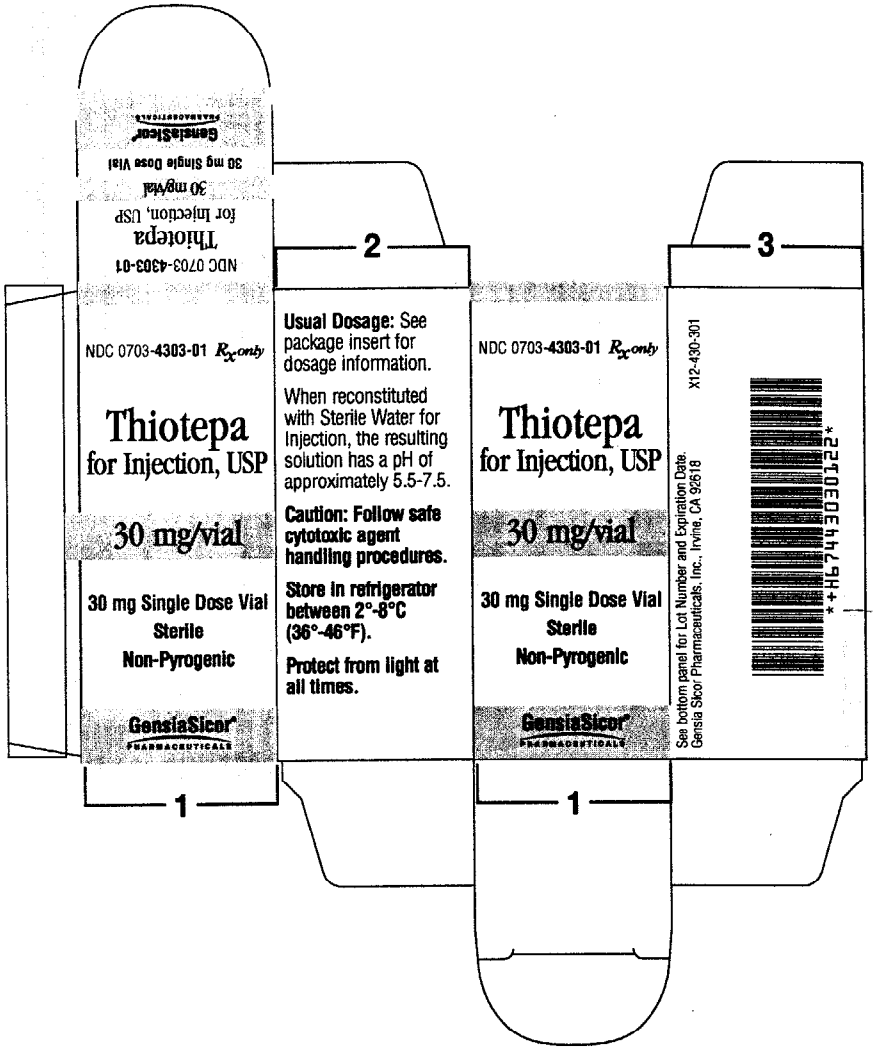


000014

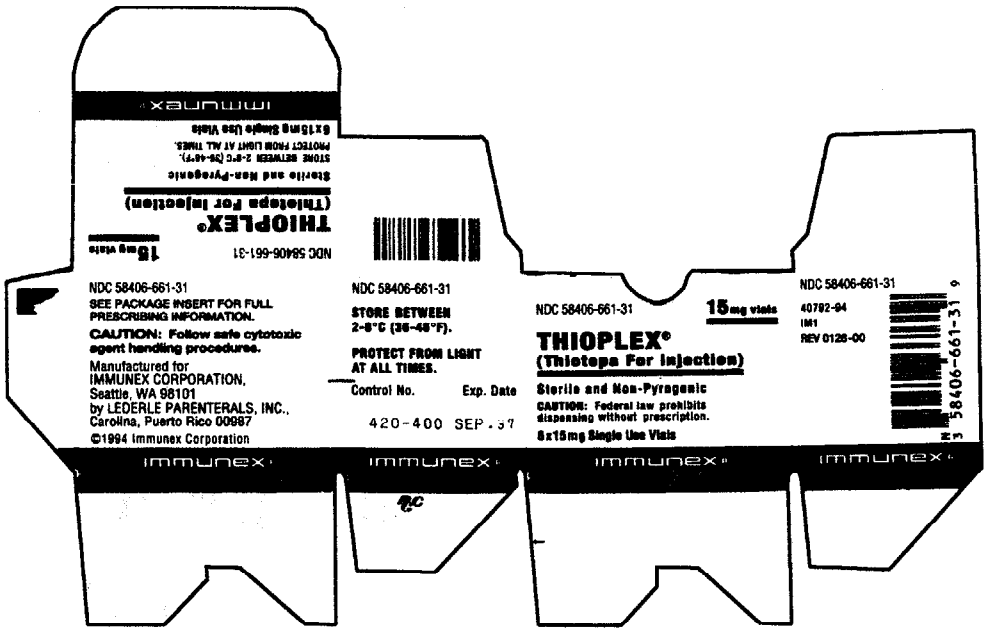
1. Revised to Gensia Sicor's logo, address, NDC number, Rx only symbol and product name.
2. Revised to read "30 mg/vial."
3. Revised to read "**30 mg Single Dose Vial.**"
4. Revised to include (from the unit carton) "**Sterile**" and "**Non-Pyrogenic.**"
5. Revised to Gensia Sicor's part number.
6. Revised to read "**Usual Dosage:** See package insert for dosage information" and include "When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5-7.5" (taken from the package insert).

5 mL UNIT CARTON--Part # X12-430-301

Gensia Sicor



Immunex



1. Revised to Gensia Sicor's logo, NDC number, Rx only symbol, product name; and to read "30 mg/vial" and "**30 mg Single Dose Vial.**"
2. Revised to read "**Usual Dosage:** See package insert for dosage information" and include "When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5-7.5" (taken from the package insert).
3. Revised to include "See bottom panel for Lot Number and Expiration Date" and to read Gensia Sicor's company name, address and bar code.

2

Attachment 2

Medical Rationale for the Proposed Product Included as Statement of Grounds

Medical Rationale

Thiotepa for Injection, 30 mg/vial

PHARMACOLOGY:

Thiotepa for Injection is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines.

INDICATIONS FOR USE:

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

DOSAGE:

Routes of administration of Thiotepa include intravenous, intracavitary, and intravesical. The recommended dosage schedules for the four routes of administration are as follows:

1. Intravenous Administration	0.3 – 0.4 mg/kg
2. Intracavitary Administration	0.6 – 0.8 mg/kg
3. Intravesical Administration	60 mg

Table 1 below illustrates the dosages in milligrams for patients with body weights ranging from 40 to 90 kg, based on the above recommended dosage schedules.

Table 1

Patient Weight (kg)	Intravenous Administration 0.3 – 0.4 mg/kg	Intracavitary Administration 0.6 –0.8 mg/kg	Intravesical Administration
40 (88 lb)	12-16 mg	24-32 mg	60 mg
50 (110 lb)	15-20 mg	30-40 mg	60 mg
60 (132 lb)	18-24 mg	36-48 mg	60 mg
70 (154 lb)	21-28 mg	42-56 mg	60 mg
80 (176 lb)	24-32 mg	48-64 mg	60 mg
90 (198 lb)	27-36 mg	54-72 mg	60 mg

RATIONALE:

The currently marketed product, Thioplex® for Injection, is available in one size – 15 mg/vial. The proposed product size, 30 mg/vial, does not pose a question of safety or effectiveness because the uses, doses, and route of administration of the proposed product are the same as those of the listed drug. The sole difference is the total amount of drug in the container. The 30 mg/vial drug product will provide the same concentration of the active and inactive ingredients as that of the listed drug product when reconstituted.

Market research indicates that the proposed 30 mg/vial product would be advantageous for practitioners since the 30 mg/vial size more closely approximates the dosing actually used for a typical patient. Additionally, the 30 mg/vial strength would reduce the number of drug containers (vials) which must be used to prepare a dose.

The availability of Thiotepa for Injection in a 30 mg/vial will offer a reduction in waste disposal compared to Thioplex® because fewer drug containers are required to prepare doses in the range set forth in the approved labeling.

As seen in Table 1, it is obvious the 30 mg/vial would be beneficial in supplying the recommended intravenous, intracavitary, and intravesical dosages from a single reconstituted vial of the product. Currently, these recommended dosages require two or more vials of the 15 mg/vial product to supply the total required dose.

Large cancer treatment centers use large quantities of the product daily, and for these centers, it is more cost efficient to use a 30 mg/vial product along with beneficial decreased product inventory.

Therefore, based on the above grounds, Thiotepa for Injection, 30 mg lyophilized/vial should be deemed suitable for an abbreviated new drug application since fewer vials are reconstituted in order to attain the required dosages, thereby, decreasing dosage preparation error and of product exposure to personnel. Additionally, the increased total dosage amounts offer a more cost-efficient product and decreases product inventory which benefits both the Health Care Facility and ultimately the patient.

SUMMARY:

In summary, the availability of Thiotepa for Injection in 30 mg/vial will offer safety, convenience and cost savings advantages over Thioplex® in 15 mg/vial. Specifically, since doses equal to or greater than 30 mg are common when using an approved regimen, the proposed 30 mg/vial size offers the advantage of convenience (saves time and money), reduces the possibility of a dosing error (because the number of vials required is less), and reduces the number of vial, syringe and needle manipulations required for reconstitution that could introduce microbial and/or particulate contamination to the sterile product.

The proposed drug product size is intended for use only as described in the **Indications and Usage** and **Dosage and Administration** sections of the draft package insert provided in the side-by-side comparison of the proposed labeling for Gensia Sicor's Thiotepa for Injection and Immunex's Thioplex® in **Attachment 1**. A copy of the innovator's labeling is provided in **Attachment 3**.

We believe that the information presented in this petition for Thiotepa for Injection supports our claim that the product size is suitable for an abbreviated new drug application.

REFERENCES:

1. Package insert for Thioplex®, Immunex Corporation. Lederle Parenterals, Inc. Issued December 1994.

Attachment 3

Immunex Corporation
Thioplex®
Package Insert

IMMUNEX Thioplex Package Insert

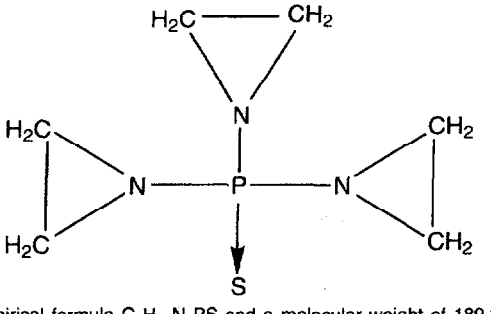
40768-94 (IM1)

THIOPLEX®
(Thiotepa For Injection)
15 mg/Vial

DESCRIPTION

THIOPLEX® (thiotepa for injection) is an ethylenimine-type compound. It is supplied as a non-pyrogenic, sterile lyophilized powder for intravenous, intracavitary or intravesical administration, containing 15 mg of thiotepa. THIOPLEX is a synthetic product with antitumor activity. The chemical name for thiotepa is Aziridine, 1,1',1''-phosphinothioylidynetris-, or Tris (1-aziridinyl) phosphine sulfide.

Thiotepa has the following structural formula:



Thiotepa has the empirical formula $C_6H_{12}N_3PS$ and a molecular weight of 189.22. When reconstituted with Sterile Water for Injection, the resulting solution has a pH of approximately 5.5 - 7.5. Thiotepa is stable in alkaline medium and unstable in acid medium.

CLINICAL PHARMACOLOGY

Thiotepa is a cytotoxic agent of the polyfunctional type, related chemically and pharmacologically to nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals which, like irradiation, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position, which severs the linkage between the purine base and the sugar and liberates alkylated guanines.

The pharmacokinetics of thiotepa and TEPA in thirteen female patients (45 - 84 years) with advanced stage ovarian cancer receiving 60 mg and 80 mg thiotepa by intravenous infusion on subsequent courses given at 4-week intervals are presented in the following table:

Pharmacokinetic Parameters (units)	Mean ± SEM			
	Thiotepa		TEPA	
	60 mg	80 mg	60 mg	80 mg
Peak Serum concentration (ng/mL)	1331 ± 119	1828 ± 135	273 ± 46	353 ± 46
Elimination half-life (h)	2.4 ± 0.3	2.3 ± 0.3	17.6 ± 3.6	15.7 ± 2.7
Area under the curve (ng/h/mL)	*2832 ± 412*	*4127 ± 668*	*4789 ± 1022*	*7452 ± 1667*
Total body clearance (mL/min)	446 ± 63	419 ± 56		

TEPA, which possesses cytotoxic activity, appears to be the major metabolite of thiotepa found in human serum and urine. Urinary excretion of ^{14}C-labeled thiotepa and metabolites in a 34-year old patient with metastatic carcinoma of the cecum who received a dose of 0.3 mg/kg intravenously was 63%. Thiotepa and TEPA in urine each accounts for less than 2% of the administered dose.

The pharmacokinetics of thiotepa in renal and hepatic dysfunction patients have not been evaluated. Possible pharmacokinetic interactions of thiotepa with any concomitantly administered medications have not been formally investigated.

IMMUNEX Thioplex Package Insert

INDICATIONS AND USAGE

Thiotepa has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

CONTRAINDICATIONS

THIOPLEX is contraindicated in patients with a known hypersensitivity (allergy) to this preparation.

Therapy is probably contraindicated in cases of existing hepatic, renal, or bone-marrow damage. However, if the need outweighs the risk in such patients, thiotepa may be used in low dosage, and accompanied by hepatic, renal and hemopoietic function tests.

WARNINGS

Death has occurred after intravesical administration, caused by bone-marrow depression from systematically absorbed drug.

Death from septicemia and hemorrhage has occurred as a direct result of hematopoietic depression by thiotepa.

Thiotepa is highly toxic to the hematopoietic system. A rapidly falling white blood cell or platelet count indicates the necessity for discontinuing or reducing the dosage of thiotepa. Weekly blood and platelet counts are recommended during therapy and for at least 3 weeks after therapy has been discontinued.

Thiotepa can cause fetal harm when administered to a pregnant woman. Thiotepa given by the intraperitoneal (IP) route was teratogenic in mice at doses ≥1 mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose (0.8 mg/kg, 27 mg/m^2), based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses ≥3 mg/kg (21 mg/m^2), approximately equal to the maximum recommended human therapeutic dose, based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately two times the maximum recommended human therapeutic dose based on body-surface area.

Effective contraception should be used during thiotepa therapy if either the patient or partner is of childbearing potential. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.

Thiotepa is a polyfunctional alkylating agent, capable of cross-linking the DNA within a cell and changing its nature. The replication of the cell is, therefore, altered, and thiotepa may be described as mutagenic. An *in vitro* study has shown that it causes chromosomal aberrations of the chromatid type and that the frequency of induced aberrations increases with the age of the subject.

Like many alkylating agents, thiotepa has been reported to be carcinogenic when administered to laboratory animals. Carcinogenicity is shown most clearly in studies using mice, but there is some evidence of carcinogenicity in man. In patients treated with thiotepa, cases of myelodysplastic syndromes and acute non-lymphocytic leukemia have been reported.

PRECAUTIONS

General

The serious complication of excessive thiotepa therapy, or sensitivity to the effects of thiotepa, is bone-marrow depression. If proper precautions are not observed thiotepa may cause leukopenia, thrombocytopenia, and anemia.

Information for Patients

The patient should notify the physician in the case of any sign of bleeding (epistaxis, easy bruising, change in color of urine, black stool) or infection (fever, chills) or for possible pregnancy to patient or partner.

Effective contraception should be used during thiotepa therapy if either the patient or the partner is of childbearing potential.

Laboratory Tests

The most reliable guide to thiotepa toxicity is the white blood cell count. If this falls to 3000 or less, the dose should be discontinued. Another good index of thiotepa toxicity is the platelet count; if this falls to 150,000, therapy should be discontinued. Red blood cell count is a less accurate indicator of thiotepa toxicity. If the drug is used in patients with hepatic or renal damage (see **CONTRAINDICATIONS** section), regular assessment of hepatic and renal function tests are indicated.

Drug Interactions

It is not advisable to combine, simultaneously or sequentially, cancer chemotherapeutic agents or a cancer chemotherapeutic agent and a therapeutic modality having the same mechanism of action. Therefore, thiotepa combined with other alkylating agents such as nitrogen mustard or cyclophosphamide or thiotepa combined with irradiation would serve to intensify toxicity rather than to enhance therapeutic response. If these agents must follow each other, it is important that recovery from the first agent, as indicated by white blood cell count, be complete before therapy with the second agent is instituted.

Other drugs which are known to produce bone-marrow depression should be avoided.

IMMUNEX Thioplex Package Insert

Carcinogenesis, Mutagenesis and Impairment of Fertility

Also see **WARNINGS** section.

Carcinogenesis

In mice, repeated IP administration of thiotepa (1.15 or 2.3 mg/kg three times per week for 52 or 43 weeks, respectively) produced a significant increase in the combined incidence of squamous-cell carcinomas of the skin, preputial gland, and ear canal, and combined incidence of lymphoma and lymphocytic leukemia. In other studies in mice, repeated IP administration of thiotepa (4 or 8 mg/kg three times per week for 4 weeks followed by a 20-week observation period or 1.8 mg/kg three times per week for 4 weeks followed by a 35-week observation period) resulted in an increased incidence of lung tumors. In rats, repeated IP administration of thiotepa (0.7 or 1.4 mg/kg three times per week for 52 or 34 weeks, respectively) produced significant increases in the incidence of squamous-cell carcinomas of the skin or ear canal, combined hematopoietic neoplasms, and uterine adenocarcinomas. Thiotepa given intravenously (IV) to rats (1 mg/kg once per week for 52 weeks) produced an increased incidence of malignant tumors (abdominal cavity sarcoma, lymphosarcoma, myelosis, seminoma, fibrosarcoma, salivary gland hemangioendothelioma, mammary sarcoma, pheochromocytoma) and benign tumors.

The lowest reported carcinogenic dose in mice (1.15 mg/kg, 3.68 mg/m^2) is approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area. The lowest reported carcinogenic dose in rats (0.7 mg/kg, 4.9 mg/m^2) is approximately 6-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Mutagenesis

Thiotepa was mutagenic in *in vitro* assays in *Salmonella typhimurium*, *E. coli*, Chinese hamster lung and human lymphocytes. Chromosomal aberrations and sister chromatid exchanges were observed *in vitro* with thiotepa in bean root tips, human lymphocytes, Chinese hamster lung, and monkey lymphocytes. Mutations were observed with oral thiotepa in mouse at doses >2.5 mg/kg (8 mg/m^2). The mouse micronucleus test was positive with IP administration of >1 mg/kg (3.2 mg/m^2). Other positive *in vivo* chromosomal aberration or mutation assays included *Drosophila melanogaster*, Chinese hamster marrow, murine marrow, monkey lymphocyte, and murine germ cell.

Impairment of Fertility

Thiotepa impaired fertility in male mice at PO or IP doses ≥0.7 mg/kg (2.24 mg/m^2), approximately 12-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa (0.5 mg) inhibited implantation in female rats when instilled into the uterine cavity. Thiotepa interfered with spermatogenesis in mice at IP doses ≥0.5 mg/kg (1.6 mg/m^2), approximately 17-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa interfered with spermatogenesis in hamsters at an IP dose of 1 mg/kg (4.1 mg/m^2), approximately 7-fold less than the maximum recommended human therapeutic dose based on body-surface area.

Pregnancy

Category D: See **WARNINGS** section.

Thiotepa can cause fetal harm when administered to a pregnant woman. Thiotepa given by the IP route was teratogenic in mice at doses ≥1 mg/kg (3.2 mg/m^2), approximately 8-fold less than the maximum recommended human therapeutic dose based on body-surface area. Thiotepa given by the IP route was teratogenic in rats at doses ≥3 mg/kg (21 mg/m^2), approximately equal to the maximum recommended human therapeutic dose based on body-surface area. Thiotepa was lethal to rabbit fetuses at a dose of 3 mg/kg (41 mg/m^2), approximately 2 times the maximum recommended human therapeutic dose based on body-surface area. Patients of childbearing potential should be advised to avoid pregnancy. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether thiotepa is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for thiotepa in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In addition to its effect on the blood-forming elements (see **WARNINGS** and **PRECAUTIONS** sections), thiotepa may cause other adverse reactions.

General: Fatigue, weakness. Febrile reaction and discharge from a subcutaneous lesion may occur as the result of breakdown of tumor tissue.

Hypersensitivity Reactions: Allergic reactions - rash, urticaria, laryngeal edema, asthma, anaphylactic shock, wheezing.

Local Reactions: Contact dermatitis, pain at the injection site.

Gastrointestinal: Nausea, vomiting, abdominal pain, anorexia.

Renal: Dysuria, urinary retention. There have been rare reports of chemical cystitis or hemorrhagic cystitis following intravesical, but not parenteral administration of thiotepa.

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Respiratory: Prolonged apnea has been reported when succinylcholine was administered prior to surgery, following combined use of thiotepa and other anticancer agents. It was theorized that this was caused by decrease of pseudocholinesterase activity caused by the anticancer drugs.

Neurologic: Dizziness, headache, blurred vision.

Skin: Dermatitis, alopecia. Skin depigmentation has been reported following topical use.

Special Senses: *Conjunctivitis.*

Reproductive: Amenorrhea, interference with spermatogenesis.

OVERDOSAGE

Hematopoietic toxicity can occur following overdose, manifested by a decrease in the white cell count and/or platelets. Red blood cell count is a less accurate indicator of thiotepa toxicity. Bleeding manifestations may develop. The patient may become more vulnerable to infection, and less able to combat such infection.

Dosages within and minimally above the recommended therapeutic doses have been associated with potentially life-threatening hematopoietic toxicity. Thiotepa has a toxic effect on the hematopoietic system that is dose related.

Thiotepa is dialyzable.

There is no known antidote for overdosage with thiotepa. Transfusions of whole blood or platelets have proven beneficial to the patient in combating hematopoietic toxicity.

DOSAGE AND ADMINISTRATION

Since absorption from the gastrointestinal tract is variable, thiotepa should not be administered *orally.*

Dosage must be carefully individualized. A slow response to thiotepa does not necessarily indicate a lack of effect. Therefore, increasing the frequency of dosing may only increase toxicity. After maximum benefit is obtained by initial therapy, it is necessary to continue the patient on maintenance therapy (1 to 4 week intervals). In order to continue optimal effect, maintenance doses should not be administered more frequently than weekly in order to preserve correlation between dose and blood counts.

Preparation and Administration Precautions: Thiotepa is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling and preparation of thiotepa. Skin reactions associated with accidental exposure to thiotepa may occur. The use of gloves is recommended. If thiotepa solution contacts the skin, immediately wash the skin thoroughly with soap and water. If thiotepa contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation of Solution: THIOPLEX (thiotepa for injection) should be reconstituted with **1.5 mL** of Sterile Water for Injection resulting in a drug concentration of approximately **10 mg/mL**. The actual withdrawable quantities and concentration achieved are illustrated in the following table:

Label Claim (mg/vial)	Actual Content (mg/vial)	Amount of Diluent to be Added (mL)	Approximate Withdrawable Volume (mL)	Approximate Withdrawable Amount (mg/vial)	Approximate Reconstituted Concentration (mg/mL)
15.0	15.6	1.5	1.4	14.7	10.4

The reconstituted solution is hypotonic and should be further diluted with Sodium Chloride Injection (0.9% sodium chloride) before use.

When reconstituted with Sterile Water for Injection, solutions of THIOPLEX should be stored in a refrigerator and used within 8 hours. Reconstituted solutions further diluted with Sodium Chloride Injection should be used immediately.

In order to eliminate haze, solutions should be filtered through a 0.22 micron filter* prior to administration. Filtering does not alter solution potency. Reconstituted solutions should be clear. Solutions that remain opaque or precipitate after filtration should not be used.

*Polysulfone membrane (Gelman's Sterile Aerodisc®, Single Use) or triton-free mixed ester of cellulose/PVC (Millipore's MILLEX®-GS Filter Unit).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Initial and Maintenance Doses: Initially the higher dose in the given range is commonly administered. The maintenance dose should be adjusted weekly on the basis of pretreatment control blood counts and subsequent blood counts.

Intravenous Administration: Thiotepa may be given by rapid intravenous administration in doses of 0.3 to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.

Intracavitary Administration: The dosage recommended is 0.6 - 0.8 mg/kg. Administration is usually effected through the same tubing which is used to remove the fluid from the cavity involved.

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Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 - 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 mL. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

Handling and Disposal: Follow safe cytotoxic agent handling procedures. Several guidelines on this subject have been published.[1-6] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

THIOPLEX® (thiotepa for injection), for single use only, is available in vials containing 15 mg of non-pyrogenic, sterile lyophilized powder, supplied as follows:

NDC 58406-661-31 - 6 x 15 mg/vial

STORAGE

Store in refrigerator between 2-8°C (36-46°F). PROTECT FROM LIGHT AT ALL TIMES.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 253(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc D, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. Ca - *A Cancer Journal for Clinicians*. Sept/Oct 1983; 258-263.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.

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